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Altered postprandial glucose metabolism and enteropancreatic hormone responses during pregnancy following Roux-en-Y gastric bypass: a prospective cohort study

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ABSTRACT

Introduction Roux-en-Y gastric bypass (RYGB) increases the risk of postprandial hypoglycemia, whereas pregnancy decreases insulin sensitivity, which could be expected to counteract hypoglycemia. We examined if RYGB performed prior to pregnancy altered the postprandial glucose metabolism and enteropancreatic hormone responses to a mixed meal test (MMT).

Research design and methods Twenty-three women with RYGB and 23 women matched on prepregnancy body mass index and parity underwent a 4-hour MMT in the first and third trimester of pregnancy with measurement of circulating levels of glucose, insulin, C-peptide, glucose-dependent insulin peptide (GIP), glucagon-like peptide 1 (GLP-1), glucagon, free fatty acids, and lactate. Biochemical hypoglycemia was defined as plasma glucose <3.5 mmol/L.

Results Women with RYGB had earlier and higher peak glucose, lower nadir glucose levels, and a higher frequency of biochemical hypoglycemia compared with women without RYGB in both the first and third trimester. The lower glucose levels were preceded by markedly elevated total GLP-1 and insulin levels in women with RYGB, whereas total GIP levels were unaltered. The glucagon levels were lower in women with RYGB. In the first trimester MMT, peak and area under the curve of total plasma GLP-1 and serum insulin levels were negatively associated with nadir plasma glucose, while the early postmeal response of plasma glucagon was positively associated with nadir plasma glucose in the third trimester.

Conclusions These results provide novel insights into the combined effects of RYGB and pregnancy on postmeal glucose metabolism and enteropancreatic hormone responses during pregnancy, and how these changes associate with an increased risk of postprandial hypoglycemia.

Trial registration number NCT03713060.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Roux-en-Y gastric bypass (RYGB) increases the risk of postprandial hypoglycemia, whereas pregnancy decreases insulin sensitivity, which in theory could counteract hypoglycemia.

WHAT THIS STUDY ADDS

⇒ Pregnancy-induced insulin resistance does not eliminate the risk of postprandial hypoglycemia caused by RYGB.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ An increased understanding of the counterregulatory mechanisms, especially the glucagon responses, could lead to prevention of hypoglycemia in this population.

⇒ Twitter summary @louiselaages *et al* from @SDCOdense found that hyperinsulinemic hypoglycemia occurred in both the first and the third trimester of pregnancy among women previously treated with RYGB despite an increase in insulin resistance during pregnancy

INTRODUCTION

Roux-en-Y gastric bypass (RYGB) increases glucose tolerance in individuals with obesity and improves glycemic control in individuals with type 2 diabetes within days from surgery, even before weight loss.[1] Altered postprandial glucose excursions following RYGB are well established with an early peak of glucose and exaggerated responses of glucagon-like peptide 1 (GLP-1) and insulin as well as greatly improved insulin sensitivity.[2–4] These changes are associated with an increased risk of hypoglycemia, also known as postbariatric hypoglycemia.[2–4] Women of childbearing age constitute about 40% of the population undergoing RYGB,[5] and the weight loss accompanying RYGB increases fertility and reduces obesity-related risks associated with pregnancy.[6–8] Pregnancy is accompanied by

decreasing insulin sensitivity with advancing gestational age.[9] Therefore, the altered glucose metabolism by RYGB might ameliorate the decreasing insulin sensitivity during pregnancy, but this is sparsely investigated. Conversely, the risk of postbariatric hypoglycemia could be expected to decrease in women with RYGB as insulin sensitivity decreases during pregnancy.[9] However, contrary to what might be expected, we found an increase in time spent with interstitial glucose <3.5 mmol/L measured by continuous glucose monitoring (CGM) during pregnancy in women with RYGB.[10] A similar increased risk of hyperinsulinemic hypoglycemia has been reported in women with polycystic ovarian syndrome and in pregnant women without bariatric surgery following a glucose load.[11 12] Different mechanisms have been proposed, such as compensatory hyperinsulinemia to insulin resistance in combination with impaired insulin clearance or insulin hypersensitivity.[11 12] To the best of our knowledge, glucose metabolism and the enteropancreatic hormone response during mixed meal test (MMT) have not been reported in pregnancy following RYGB.[13]

Within normal physiology, the initial counterregulatory response to hypoglycemia consists of the release of glucagon and epinephrine as the plasma glucose levels drop below 3.8 mmol/L.[14] Increased glucagon is expected to augment hepatic glucose production, but Salehi *et al*[15] showed a reduced and shortened postprandial glucose production in response to glucagon in postbariatric individuals without diabetes. Following the postprandial nadir of glucose, glucagon did not increase further in individuals with RYGB.[16 17] Furthermore, the postprandial glucagon responses have been shown to be identical among individuals with and without hypoglycemia, suggesting α-cell dysfunction.[18] Similar studies have not been conducted during pregnancy.

Data regarding postbariatric hypoglycemia in pregnancy are sparse; nevertheless, hypoglycemia appears to be common.[13] Therefore, we investigated the postprandial glucose metabolism following MMT in early and late pregnancy in a cohort of women treated with RYGB prior to pregnancy and compared the results with those obtained in non-operated matched pregnant women. The MMTs were performed in both early and late pregnancy to investigate changes during pregnancy. Furthermore, we investigated the enteropancreatic hormone responses elicited by the MMTs.

RESEARCH DESIGN AND METHODS

Study population

This study was a prospective, observational study performed as part of the Bariatric surgery And consequences for Mother and Baby In pregnancy (BAMBI) study registered at ClinicalTrials.gov (NCT03713060).[19] We recruited the BAMBI cohort from April 2019 to November 2021 at Odense University Hospital (Odense, Denmark). We aimed to include pregnant women treated with RYGB prior to pregnancy and for each woman, a pregnant woman without a history of bariatric surgery matched on age, parity, and prepregnancy body mass index (BMI).

We included women aged 18–45 years with singleton pregnancies. The women were non-smokers, did not consume alcohol, and did not have type 2 diabetes, nor other severe medical or psychiatric illness. Women were eligible for inclusion even if they had experienced gestational diabetes mellitus (GDM) in a previous pregnancy. All controls underwent a 2-hour 75 g oral glucose tolerance test (OGTT) at 24 weeks of gestation, while women with RYGB were screened for GDM by postmeal self-monitoring of blood glucose according to Danish national standards as part of their routine follow-up in the outpatient clinic.[20] Women with pregnancies resulting in miscarriage, stillbirth, termination, or delivery of a phenotypically abnormal infant were excluded. Furthermore, we excluded women with overt type 2 diabetes at inclusion.

Mixed meal test

The MMT was performed twice in each pregnancy, in the first trimester (gestational week 12–14) and in the third trimester (gestational week 34) following an overnight fast (10 hours). The women were instructed to refrain from strenuous physical activity for 3 days prior to the MMT.

At time 0–15 min, the women consumed a liquid mixed meal consisting of 200 mL Nutridrink (300 kcal, 49 E% carbohydrate, 16 E% protein and 35 E% fat, Nutricia, Allerød, Denmark). Blood samples were drawn at t=0, 30, 60, 90, 120, and 240 min. Plasma samples were collected in chilled EDTA tubes and serum samples in tubes lined with clot activator. All samples were immediately inverted 10 times, and afterwards plasma samples were centrifuged instantly at 4°C, whereas serum samples were centrifuged after 30 min.

Biochemical hypoglycemia was defined as plasma glucose levels below 3.5 mmol/L during the MMT according to an international consensus on CGM-derived glucose targets in pregnancy.[21]

Assays

Plasma glucose and lactate were analyzed bedside using an ABL800 Flex analyzer (Radiometer, Denmark). The remaining plasma was stored at −80°C until analysis. Serum insulin and C-peptide were analyzed simultaneously using a combined immunoassay on a cobas e 411 analyzer (Roche Diagnostics, Switzerland). Plasma free fatty acids (FFA) were analyzed using immunoassay on the cobas 8000 (Roche Diagnostics, Switzerland). Total plasma GLP-1 and glucose-dependent insulin peptide (GIP) were analyzed with radioimmunoassay (RIA) using C-terminally directed antisera 89390 and 80867, respectively.[22 23] Finally, plasma glucagon was analyzed using the Mercodia Glucagon ELISA (Mercodia, Sweden) with the extended wash protocol, which includes an extra washing step reducing cross-reactivity to glicentin and

proglucagon.[24] Plasma glucagon levels below the detection rate of 0.8 pmol/L were expressed as 0.8 pmol/L.

Calculations

We calculated fasting hepatic insulin clearance as the ratio of the fasting serum C-peptide and insulin levels based on the assumption that C-peptide and insulin are secreted equimolarly, whereas C-peptide is not subjected to hepatic first-pass metabolism.[25] The updated homeostatic model assessment for insulin resistance (HOMA2-IR) was calculated based on fasting serum C-peptide and obtained using the calculator (https://www.dtu.ox.ac.uk/homacalculator/). Insulin sensitivity was assessed by the Stumvoll index calculated as $0.156-(0.0000459\times\text{serum insulin}_{t=120\ min})-(0.000321\times\text{fasting insulin})-(0.00541\times\text{glucose}_{t=120\ min})$.[26 27] Finally, β-cell function was assessed by the oral disposition index calculated as $\Delta\text{c-peptide}_{0-30}/\Delta\text{glucose}_{0-30}\times 1/\text{fasting insulin}$ as well as by the insulinogenic index calculated as $\Delta\text{insulin}_{0-30}/\Delta\text{glucose}_{0-30}$.[28]

Adipose tissue insulin resistance (Adipo-IR) was calculated by multiplying fasting FFA and fasting insulin.

Total area under the curve (AUC) over the 240 min was calculated using the trapezoidal method. For glucagon, the early postmeal response was calculated as the AUC for the initial 60 min of the MMT.

Statistical analyses

The primary outcome of the study was nadir plasma glucose levels in response to an MMT. To the best of our knowledge, MMTs in pregnant women with RYGB have not been reported. Based on MMTs in women before and 1 year after RYGB, an SD of 0.5 mmol/L in plasma glucose was expected.[29] In order to provide a power >80% and a significance of 5%, 16 women should be included in each group.

We used the Research Electronic Data Capture electronic data capture tools hosted at Open Data Explorative Network, Odense University Hospital (Odense, Denmark) for collection and management of data.[30 31] The statistical analyses were performed by either Stata V.17 (StataCorp, College Station, Texas, USA) or IBM SPSS Statistics for Windows V.28 (IBM, Armonk, New York, USA). Analyses were performed comparing differences between the groups at first and third trimester using the Wilcoxon rank-sum test and differences in changes (delta-values) between groups from first to third trimester using the analysis of covariance test. Differences within the groups from the first to the third trimester were compared using the Wilcoxon signed-rank test. Categorical variables were compared by Fisher's exact test. The relationships between nadir plasma glucose and continuous variables were examined by calculation of correlation coefficients using partial correlation to control for potential confounders. Median values and IQRs were calculated and reported for continuous variables. Significance was accepted at the $p\leq 0.05$ level.

Data and resource availability

The datasets generated and analyzed during the current study are not publicly available due to Danish data protection regulation but are available from the corresponding author on reasonable request. No applicable resources were generated or analyzed during the current study.

RESULTS

As previously reported,[10] 23 women treated with RYGB were matched with 23 pregnant women on BMI (32 kg/m^2 (IQR 27–39) vs 33 kg/m^2 (IQR 28–40)) and parity. Women with RYGB were older than the controls (35 years (IQR 31–38) vs 30 years (IQR 26–32), p<0.01). The median surgery-to-conception interval was 30 months (IQR 15–89), and the women reduced their BMI from 45 kg/m^2 (IQR 42–54) to a nadir BMI of 28 kg/m^2 (IQR 24–33) corresponding to a total weight loss of 35% (IQR 31–45). One woman in each group had GDM in a previous pregnancy. During pregnancy, two women (9%) with RYGB and one (4%) control were diagnosed with GDM according to Danish national standards by self-monitoring of blood glucose profiles or OGTT, respectively.

Postprandial glucose metabolism and enteropancreatic hormone responses

The profiles of glucose and the enteropancreatic hormones did not change markedly in either group during pregnancy, but differed between groups (figures 1, 2, tables 1, 2). Women with RYGB presented with lower fasting plasma glucose, higher postprandial peak plasma glucose, and lower nadir plasma glucose, and both peak and nadir were observed earlier among women with RYGB compared with controls in both trimesters (all p<0.01) (table 1 and figure 1A,B). While nine (39%) and five (24%) of the women with RYGB had nadir glucose levels below 3.5 mmol/L in the first and third trimester, respectively, one (4%) and none of the controls experienced biochemical hypoglycemia in the first and third trimester, demonstrating a higher frequency of biochemical hypoglycemia in women with RYGB (all p<0.05).

Fasting serum levels of insulin and C-peptide were lower (all p<0.01), whereas the peak levels of both were markedly elevated (all p<0.01) among women with RYGB compared with controls in both trimesters (table 1 and figure 1C–F). The fasting-derived insulin resistance index, HOMA2-IR, was lower (p<0.01) and the MMT-derived insulin sensitivity index, Stumvoll, was higher (p<0.01) in women with RYGB compared with controls in both trimesters (table 1). Fasting levels of serum insulin and C-peptide increased in both groups from the first to the third trimester (all p<0.001). In accordance, HOMA2-IR increased less during pregnancy among the women with RYGB compared with the controls (p<0.05). Fasting insulin clearance was higher in women with RYGB compared with controls in both trimesters.

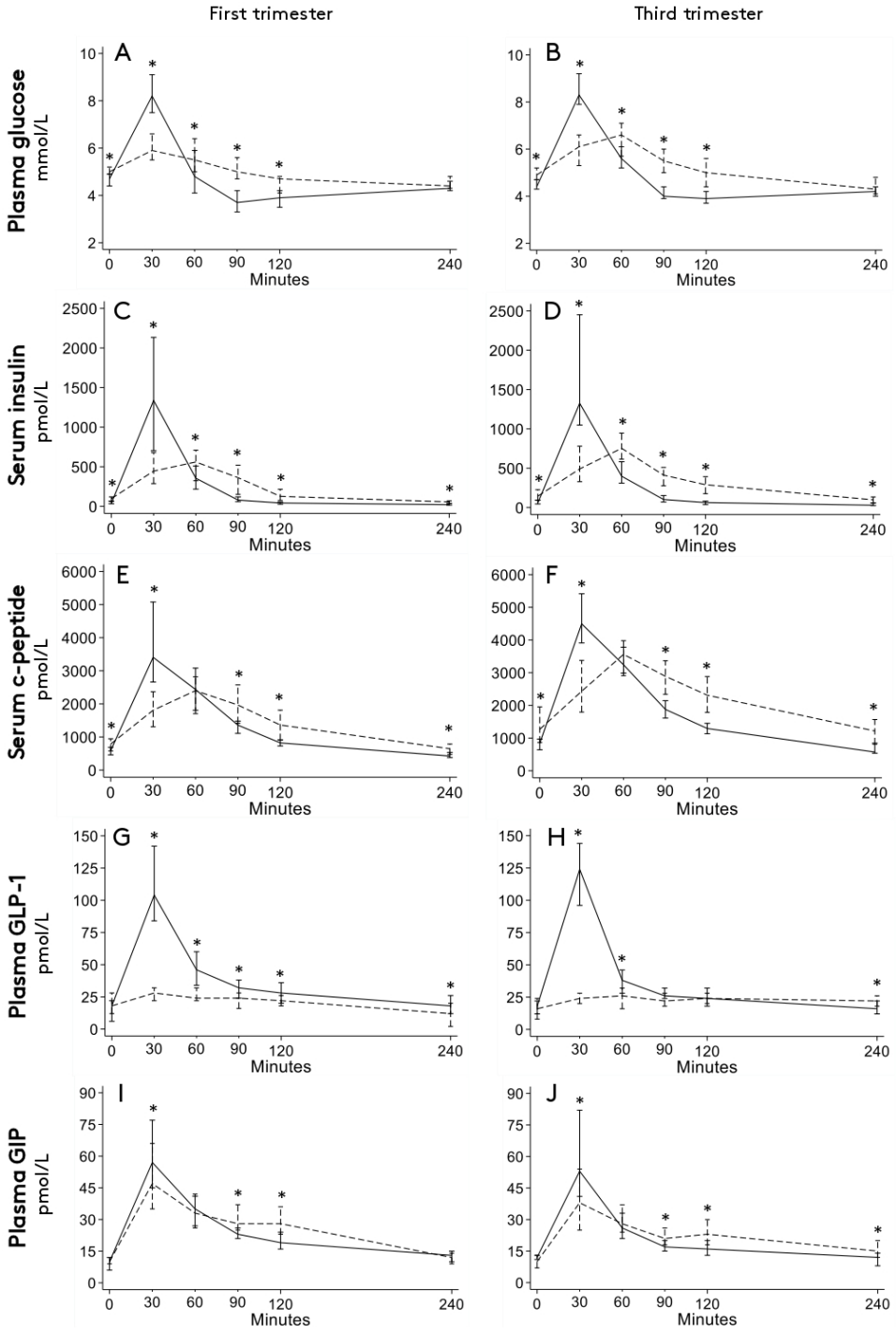

Figure 1 Median glucose (A, B), insulin (C, D), C-peptide (E, F), GLP-1 (G, H), and GIP (I, J) with IQR during mixed meal test performed in the first and third trimester of pregnancy. Performed in women treated with RYGB, solid line (n_{first}=23, n_{third}=21), and matched controls, dashed line (n_{first}=23, n_{third}=23). *P<0.05, women with RYGB versus controls. GIP, glucose-dependent insulin peptide; GLP-1, glucagon-like peptide 1; RYGB, Roux-en-Y gastric bypass.

The postmeal total GIP responses were similar between the groups apart from slightly higher peak levels among the women with RYGB in the third trimester (p=0.02) due to a decrease during pregnancy among the controls (p<0.05) (table 1 and figure 1I,J). On the other hand, peak levels of total GLP-1 were more than threefold elevated, and AUC of total GLP-1 almost twofold higher in both the first and the third trimester in women with RYGB compared with controls (all p<0.01) (table 1 and figure 1G,H). No changes in total GLP-1 levels were seen between the first and the third trimester within the groups.

The plasma glucagon levels at nadir glucose and the 240 min AUC of plasma glucagon were lower in women with RYGB compared with controls in the first trimester (all p<0.01), whereas fasting plasma glucagon and

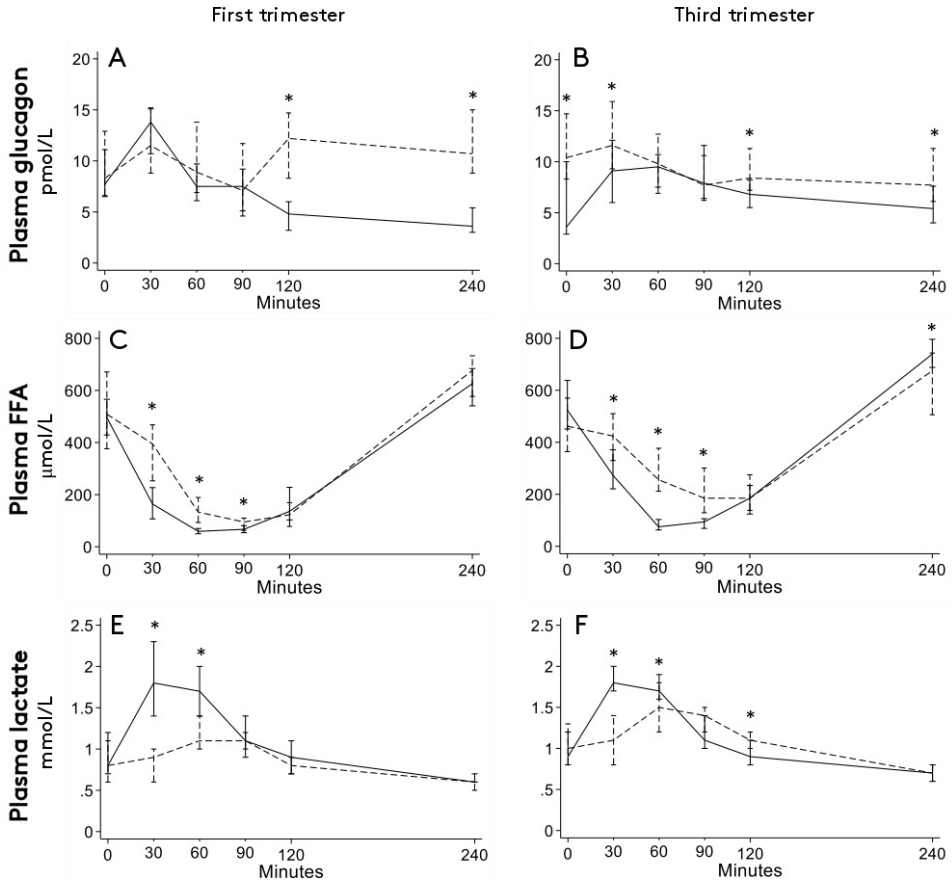

Figure 2 Median glucagon (A, B), FFAs (C, D) and lactate (E, F) with IQR during mixed meal test performed in the first and third trimester of pregnancy. Performed in women treated with RYGB, solid line (n_{first}=23, n_{third}=21), and matched controls, dashed line (n_{first}=23, n_{third}=23). *P<0.05, women with RYGB versus controls. FFA, free fatty acid; RYGB, Roux-en-Y gastric bypass.

240 min AUC of plasma glucagon were lower in women with RYGB compared with controls in the third trimester (p<0.05) (table 2 and figure 2A,B). The early postmeal glucagon response, 60 min AUC of plasma glucagon, decreased among the women with RYGB from the first to the third trimester (p=0.02).

Nadir plasma FFA levels were lower (p<0.05) and observed earlier (p<0.01) in women with RYGB compared with controls in both trimesters (table 2 and figure 2C,D). The increase of nadir plasma FFA from the first to the third trimester was lower among the women with RYGB compared with the controls (table 2). Adipo-IR was lower in women with RYGB compared with controls in both trimesters (all p<0.01), but increased slightly only in women with RYGB from the first to the third trimester (p<0.01). Peak levels of lactate were higher among the women with RYGB compared with the controls in both trimesters (all p<0.01) (table 2 and figure 2E,F).

Correlation analyses

To explore the potential role of altered enteropancreatic hormone responses in postbariatric biochemical hypoglycemia during different periods of pregnancy, we examined the correlations between nadir plasma glucose and circulating levels of insulin, total GLP-1, total GIP, and glucagon during the MMT in women with RYGB. In the first trimester, nadir plasma glucose correlated inversely with peak total GLP-1 (r=−0.51; p=0.03), AUC of total GLP-1 (r=−0.52; p=0.02), peak serum insulin (r=−0.57; p=0.01), AUC of serum insulin (r=−0.47; p=0.04), and insulin at nadir glucose (r=−0.46; p<0.05), when adjusted for age, prepregnancy BMI, gestational weight gain at the time of MMT, and percentage of total weight loss, whereas no correlations were observed between nadir plasma glucose and circulating plasma glucagon. Conversely, in the third trimester, we observed no significant associations between nadir plasma glucose and serum insulin or plasma GLP-1, whereas 60 min AUC of plasma glucagon (r=0.82; p<0.0001) correlated positively with nadir plasma glucose after adjusting for the abovementioned potential confounders.

DISCUSSION

To the best of our knowledge, this is the first longitudinal characterization of the postprandial glucose metabolism and enteropancreatic hormone responses to a MMT in pregnancy following RYGB. The postprandial profiles of glucose and the enteropancreatic hormones did not change markedly during pregnancy. Compared with

Table 1 Postprandial glucose metabolism and enteropancreatic responses to a mixed meal test during pregnancy in women with RYGB compared with matched controls

	RYGB			Controls			
	First trimester	Third trimester	Difference	First trimester	Third trimester	Difference	
	23 (100)	21 (91)	21 (91)	23 (100)	23 (100)	23 (100)	P value
Plasma glucose, mmol/L							
Fasting	4.7 (4.4–4.9)	4.4 (4.3–4.7)	−0.3 (−0.5–0)*	5.0 (4.9–5.2)†	4.9 (4.7–5.2)†	−0.2 (−0.5–0.3)	0.71
Nadir	3.7 (3.3–4.1)	3.9 (3.5–4.0)	0.2 (0–0.5)*	4.2 (4.1–4.4)†	4.2 (4.0–4.5)†	0 (−0.3–0.3)	0.32
Time of nadir glucose, min	90 (90–120)	120 (90–120)	30 (0–45)*	120 (90–240)†	240 (120–240)†	15 (0–120)*	0.34
Nadir <3.5 mmol/L	939	524	−4 (−17)	14†	0 (0)†	−1 (−4)	
Peak value	8.2 (7.5–9.1)	8.3 (7.9–9.2)	0.7 (−0.5–1.1)	6.3 (5.5–6.7)†	6.6 (5.9–7.1)†	0.4 (−0.4–1.0)	0.91
Time of peak glucose, min	30 (30–30)	30 (30–30)	0 (0–0)	30 (30–60)†	60 (30–60)†	0 (0–30)	0.13
$AUC_{glucose\ 240}$, mmol/L·min	1137 (1083–1194)	1160 (1109–1187)	32 (−1–96)	1179 (1137–1250)†	1230 (1154–1323)†	41 (−38–134)	0.95
Serum insulin, pmol/L							
Fasting	40 (32–65)	57 (45–93)	13 (7–33)*	97 (63–119)†	144 (94–226)†	42 (14–70)*	0.15
Peak value	1337 (703–2134)	1326 (1049–2451)	222 (−92–625)*	603 (456–808)†	781 (662–963)†	163 (−29–332)*	0.85
Value at nadir glucose	78 (51–110)	63 (38–85)	−1 (−21–14)*	92 (62–123)	102 (67–172)†	26 (−39–82)	0.12
$AUC_{insulin\ 240}$, nmol/L·min	66 (38–95)	68 (51–104)	17 (2–25)*	51 (40–67)	79 (63–108)	23 (10–43)*	0.44
Fasting insulin clearance	13 (11–16)	12 (10–16)	0 (−3–2)	8 (7–10)†	9 (8–10)†	1 (0–2)	0.41
Insulinogenic index	421 (235–647)	354 (288–505)	14 (−115–64)	419 (311–750)	386 (258–657)	38 (−171–173)	0.59
Oral disposition index	19 (15–30)	16 (11–23)	−6 (−11–−1)	16 (8–24)	9 (5–14)†	−3 (−11–2)*	0.73
Stumvoll	121 (111–124)	112 (99–120)	−6 (−11–−1)	94 (83–107)†	65 (40–95)†	−22 (−42–−9)	0.06
HOMA2–IR	1.3 (1.0–1.5)	1.8 (1.3–2.1)	0.4 (0.3–0.06)*	1.8 (1.3–2.1)†	2.7 (1.9–4.2)†	1.0 (0.6–1.5)*	0.05
Serum C–peptide, pmol/L							
Fasting	590 (460–685)	837 (642–969)	219 (154–289)*	788 (578–946)†	1268 (865–1954)†	486 (312–673)*	0.05
Peak value	3408 (2739–5087)	4495 (3909–5415)	967 (446–1355)*	2566 (2133–3011)†	3560 (2911–4059)†	1032 (468–1327)*	0.96
$AUC_{C-peptide\ 240}$, nmol/L·min	320 (266–395)	449 (378–496)	134 (87–177)*	345 (245–392)	533 (455–669)	207 (140–240)*	0.24
Plasma GLP–1, pmol/L							
Fasting	18 (6–22)	18 (12–22)	4 (−3–12)	18 (12–28)	16 (8–24)	2 (−14–10)	0.22
Peak value	104 (84–142)	124 (96–144)	16 (−17–44)	30 (26–34)†	30 (24–38)†	2 (−8–10)	0.30
AUC_{GLP-1}, pmol/L·min	8670 (7500–10 860)	8820 (7290–10 140)	1140 (−1080–1935)	4980 (4620–5430)†	5820 (4290–6690)†	1170 (−750–1920)*	0.30
Plasma GIP, pmol/L							
Fasting	10 (6–12)	12 (11–13)	1 (−2–6)	10 (9–12)	10 (7–13)	0 (−4–3)	0.34
Peak value	57 (45–77)	53 (41–82)	−5 (−12–6)	47 (39–66)	39 (30–54)†	−9 (−17–−1)*	0.99
$AUC_{GIP\ 240}$, pmol/L·min	5955 (5115–6945)	4935 (3840–6285)	−555 (−1365–308)*	5970 (5445–7800)	5445 (4590–6780)	−900 (−1440–330)*	0.79

Data are presented as medians (IQRs) or numbers (%).
P values referring to the difference in changes between groups from first to third trimester.
*P<0.05 third versus first trimester within the groups.
†P<0.05 women with RYGB versus controls in each trimester.
AUC, area under the curve; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HOMA2-IR, homeostatic model assessment for insulin resistance; RYGB, Roux-en-Y gastric bypass.

Table 2 Glucagon, FFAs, and lactate response to a mixed meal test during pregnancy in women with RYGB compared with matched controls–

	RYGB			Controls			
	First trimester	Third trimester	Difference	First trimester	Third trimester	Difference	
	23 (100)	21 (91)	21 (91)	23 (100)	23 (100)	23 (100)	P value
Plasma glucagon, pmol/L							
Fasting	7.7 (6.5–11.1)	3.6 (2.9–10.0)	−4.1 (−6.3–2.2)*	8.3 (6.6–12.9)	10.4 (8.3–14.7)†	1.8 (−0.2–3.2)*	<0.01
Peak value	13.8 (10.7–15.8)	10.7 (9.1–14.2)	−2.4 (−4.7–−0.5)	13.8 (11.5–16.9)	13 (10.1–16.1)	−0.5 (−4.1–1.7)	0.93
Value at nadir glucose	7.2 (3.6–9.4)	6.8 (4.7–8.2)	0.0 (−1.9–2.9)	11.2 (7.1–15.0)†	7.7 (6.1–11.0)	−1.8 (−7.3–1.8)	0.14
$AUC_{Glucagon\ 240}$, pmol/L·min	1542 (1329–1884)	1694 (1266–2136)	303 (−298–506)	2555 (1986–392)†	2123 (1742–2822)†	−321 (−857–390)*	0.12
$AUC_{Glucagon\ 60}$, pmol/L·min	630 (578–803)	440 (368–645)	−246 (−263–−−96)*	632 (504–821)	644 (546–872)†	68 (−116–96)	0.05
Plasma FFA, µmol/L							
Fasting	496 (429–566)	524 (451–638)	71 (−26–147)*	509 (376–671)	462 (364–570)	−119 (−178–93)*	0.06
Nadir value	56 (41–69)	72 (62–98)	25 (3–40)*	67 (55–105)†	175 (118–214)†	84 (55–151)*	<0.01
Time of nadir FFA, min	90 (60–90)	60 (60–90)	0 (−30–0)	90 (90–120)†	120 (90–120)†	0 (0–30)*	0.07
$AUC_{FFA\ 240}$, µmol/L·min	66 (61–71)	79 (68–92)	12 (−1–21)*	78 (63–88)	90 (78–98)	16 (3–22)*	0.94
Adipo–IR, mmol/L·pmol/L	19 (14–33)	31 (25–48)	13 (3–16)*	53 (29–66)†	62 (45–102)†	13 (−13–45)	0.57
Plasma lactate, mmol/L							
Fasting	0.8 (0.7–1.2)	0.9 (0.8–1.2)	0 (−0.4–0.2)	0.8 (0.6–1.1)	1.0 (0.8–1.3)	0.2 (−0.2–0.5)	0.76
Peak value	1.8 (1.6–2.3)	2.0 (1.8–2.1)	0 (−0.2–0.2)	1.3 (1.1–1.5)†	1.6 (1.3–1.8)†	0.3 (0–0.5)*	0.22
$AUC_{lactate\ 240,}$ mmol/L·min	243 (207–309)	275 (246–303)	15 (−41–58)	204 (189–221)†	267 (236–290)	57 (23–104)*	0.04

Data are presented as medians (IQRs) or numbers (%).
P values referring to the difference in changes between groups from first to third trimester.
*P<0.05 third versus first trimester within the groups.
†P<0.05 women with RYGB versus controls in each trimester.
Adipo-IR, adipose tissue insulin resistance; AUC, area under the curve; FFA, free fatty acid; RYGB, Roux-en-Y gastric bypass.

the controls, the women with RYGB were less insulin resistant, as evaluated by fasting insulin, the Stumvoll index, and HOMA2-IR throughout pregnancy. However, similar to the controls, they experienced an increase in fasting insulin and HOMA2-IR from the first to the third trimester. In spite of this pregnancy-induced increase in fasting-derived indices of insulin resistance, the frequency of biochemical hypoglycemia in women with RYGB was higher than in controls in both trimesters. Nadir plasma glucose was preceded by markedly elevated levels of total GLP-1 and insulin in women with RYGB, and these associations were significant in the first trimester but lost in the third trimester, where elevated plasma glucagon correlated with increased nadir glucose levels. Glucagon levels were lower in women with RYGB.

The profiles of glucose, insulin, C-peptide, total GLP-1, and total GIP among women with RYGB in the BAMBI cohort resembled the previously reported profiles in non-pregnant individuals treated with RYGB.[2–4 15] Likewise, the prevalence of biochemical hypoglycemia corresponded to the prevalence found by Kefurt *et al*[32] in a cohort consisting predominantly of women with a similar presurgery and postsurgery BMI, although slightly older and with a longer surgery-to-test interval. As in controls, insulin resistance increased in women with RYGB during pregnancy. However, this was not accompanied by a significantly lower frequency of biochemical hypoglycemia in the third trimester of pregnancy. Thus, even though the pregnancy-induced insulin resistance alters glucose metabolism from the first to the third trimester, these alterations do not seem to protect against the increased risk of postprandial biochemical hypoglycemia elicited by RYGB.

In this study, HOMA2-IR was lower in both the first and the third trimester of pregnancy among the women with RYGB compared with BMI-matched controls. This is in accordance with the findings by Svane *et al*[33] showing lower HOMA-IR among individuals with RYGB compared with BMI-matched controls. They investigated individuals with RYGB without a history of type 2 diabetes and normal glucose tolerance. As both control groups were BMI-matched, RYGB could seem to improve the insulin sensitivity beyond the improvement caused by the weight loss. However, the reliability of HOMA as a surrogate measure of insulin sensitivity in individuals with RYGB has been questioned owing to increased insulin clearance, as was also evident in the current study.[34] To reduce the influence of the increased insulin clearance, we based our HOMA2-IR calculation on fasting serum C-peptide. In addition, the lower degree of insulin resistance in the pregnant women with RYGB was confirmed by increased insulin sensitivity (Stumvoll index) during the MMT. In contrast, a recent prospective study found no differences in the metabolic benefits, including improved insulin sensitivity after an ~18% wt loss achieved by either RYGB or diet, suggesting that the metabolic benefits were related to weight loss itself.[35] In that study, insulin sensitivity was measured using hyperinsulinemic euglycemic pancreatic clamp. Further studies are needed to establish if these differential findings are due to differences in study design, magnitude of weight loss after RYGB or methods of assessing insulin sensitivity.

As expected in normal pregnancy,[9] fasting insulin, peak insulin, AUC of insulin, and HOMA2-IR increased during pregnancy among the controls. Insulin clearance was increased among the women with RYGB as previously reported in non-pregnant populations with RYGB,[36 37] but did not change during pregnancy in either group. Therefore, an increase in HOMA2-IR could be interpreted as an increase in insulin resistance. During pregnancy, women with RYGB became more insulin resistant yet to a lesser extent than the controls.

Mean fasting plasma glucose decreased slightly during pregnancy among the women with RYGB. In individuals with type 2 diabetes, prediabetes, or obesity, mean fasting plasma glucose has been shown to decrease gradually after bariatric surgery.[2 4] Ilesanmi *et al*[2] showed that mean fasting plasma glucose decreased progressively from presurgery to 1-year postsurgery and stabilized between 1 and 2 years postsurgery in parallel with weight stabilization. Among the women with RYGB in the BAMBI study, 30 months had passed from surgery until pregnancy and inclusion, and the gestational weight gain was about 10 kg.[10] Thus, the detected decrease in plasma glucose is not likely to be explained by the time lag of about 20–22 weeks between the two measurements.

Following RYGB, nutrients are delivered readily to the GLP-1 secreting L-cells in the terminal ileum and colon,[38] and GLP-1 has been suggested as the main driver behind hypoglycemia during mid-pregnancy OGTT.[39] In accordance, we found increased peak total GLP-1 levels among women with RYGB as compared with the controls in both trimesters. Furthermore, in the first trimester, we found that peak/AUC of serum insulin and plasma total GLP-1 levels correlated inversely with nadir plasma glucose after adjustment for potential confounders. Intriguingly, these correlations were lost in the third trimester, and replaced by significant correlation between early AUC of plasma glucagon and nadir plasma glucose levels. These results are in alignment with the study by Ilesanmi *et al*[2] who found that peak GLP-1 and glucagon levels during the MMT were positively and negatively associated with increased time spent in hypoglycemia during CGM, respectively, in individuals with RYGB who had prediabetes or type 2 diabetes prior to RYGB.[2] As proposed by Øhrstrøm *et al*,[17] counterregulatory responses could modulate the risk of postbariatric biochemical hypoglycemia in addition to the increase in GLP-1. Our results indicate a shift in the role of elevated GLP-1/insulin versus lower glucagon in the risk of postbariatric biochemical hypoglycemia from the first to the third trimester in women with RYGB. Further studies are warranted to establish these findings and potential underlying mechanisms.

Even though a higher percentage of women with RYGB had biochemical hypoglycemia during the MMT compared with controls, the early postmeal response of

plasma glucagon, 60 min AUC of glucagon, decreased among the women with RYGB while it was unchanged among the controls during pregnancy. The glucagon levels observed in the women with RYGB in the first trimester of our study are in line with the levels reported in previous studies of postbariatric individuals showing an early postprandial peak and the absence of an increase in plasma glucagon following glucose nadir.[16–18 33] In the third trimester, both the early postprandial peak in plasma glucagon and the increase following glucose nadir appeared to be absent among the women with RYGB in our study. As speculated in the non-pregnant population, abnormal α-cell function could contribute to postbariatric biochemical hypoglycemia with deterioration in late pregnancy.[18 40–42]

GIP is secreted by the K-cells of the duodenum and proximal jejunum,[43] and thus, most GIP-secreting cells are bypassed by the RYGB. In previous studies where GLP-1 was blocked, GIP failed to increase the postprandial insulin response to ingested glucose.[38 44] Consequently, GIP is not believed to play an important role in postbariatric biochemical hypoglycemia.[44 45] Similar to the findings by Leutner *et al*,[39] who investigated pregnant women with RYGB by OGTT, we found equal responses of total GIP elicited by the MMT among women with RYGB and controls in both trimesters.

A strength of the study is the inclusion of a BMI-matched control group. The liquid meal was chosen in order to ensure ingestion of the same meal over the course of time. Recently, Hedbäck *et al*[46] showed that liquid and solid meals with identical macronutrient composition result in similar postprandial glucose responses for both subjects with RYGB and non-surgical controls. They concluded that a liquid meal is suitable for the assessment of the glycemic and enteropancreatic response in both individuals with RYGB and non-surgical controls. Finally, the use of the new assay protocol of the Mercodia Glucagon ELISA is a strength. The new assay protocol reduces cross-reactivity with glicentin and proglucagon, which otherwise interferes with measurements particularly in individuals with RYGB, but makes comparisons with previous studies using other assay protocols difficult.

Our prespecified time points for blood sampling may limit our results regarding the exact determination of nadir plasma glucose levels and counterregulatory increases in plasma glucagon. Thus, both could happen later than 120 min. Jørgensen *et al*[4] showed that the lowest glucose levels occur between 90 and 120 min in response to an MMT in normal glucose-tolerant individuals with RYGB, but later (180–240 min) in individuals with type 2 diabetes after RYGB. Apart from the two women with RYGB and one among the controls diagnosed with GDM, the women were perceived as normal glucose tolerant. Furthermore, Jørgensen *et al*[4] did not report major changes in plasma glucagon after 180 min. Another potential limitation is the lack of measures of other glucose counterregulatory hormones. However, in a study of non-pregnant individuals with RYGB, cortisol and norepinephrine levels did not increase unless glucose was lowered by glucose-lowering drugs.[17] Insulin resistance increases with age, and, therefore, the difference in age could potentially also affect our results.[47] However, the women with RYGB were older, and thus, the reported differences in insulin resistance and biochemical hypoglycemia between the groups would be expected to be attenuated rather than overestimated. The correlation analyses were adjusted for age.

In conclusion, we demonstrated that pregnant women with RYGB had similar distinct profiles of postprandial glucose and the enteropancreatic hormones in response to a MMT in the first and the third trimester of pregnancy. These profiles resembled previously shown profiles for non-pregnant individuals with RYGB. Postbariatric biochemical hypoglycemia occurred in both the first and the third trimester of pregnancy despite an increase in insulin resistance during pregnancy. As such, pregnancy seems to neither aggravate nor ameliorate the risk of biochemical hypoglycemia as assessed by MMT. During the first trimester MMT, peak and AUC of total plasma GLP-1 and serum insulin levels were negatively associated with nadir plasma glucose, while these associations were absent in the third trimester and replaced by a positive association between the early postmeal plasma glucagon response and nadir plasma glucose. Thus, an increased understanding of the counterregulatory mechanisms, as illustrated by glucagon responses, could lead to prevention of hypoglycemia in this population.

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access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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